THE ROLE OF C-REACTIVE PROTEIN IN FEVER WITHOUT FOCUS IN CHILDREN BETWEEN 1 TO 36 MONTHS OF AGE

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CERTIFICATE

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CONTENTS

INTRODUCTION

FEVER WITHOUT FOCUS

Fever without localizing signs or symptoms, usually of acute onset and present for less than one week.[1]It is more common in children less than 36 months of age. [1]

FEVER OF UNKNOWN ORIGIN

Children with fever in whom cause could not be identified after 3 week of evaluation as an outpatient or after 1 week of evaluation in hospital.[1]

Fever is a common manifestation of infectious diseases but is not predictive of severity.[1] Many common viral and bacterial infections are usually benign in normal hosts and respond well to appropriate antimicrobial or supportive therapy. Other infections such as sepsis, meningitis, pneumonia, osteoarticular infections, pyelonephritis, if untreated, may have significant morbidity or mortality. They are considered to be serious bacterial infections.[1]

Most febrile episodes in a normal host can be diagnosed by a careful history and physical examination and require few if any

laboratory tests.[2] Febrile patients at increased risk for serious bacterial infections are neonates, infants less than three months children between 3 months to 36 months, children with hyperpyrexia [3] and immunocompromised patients. Approximately 30% of febrile children between 3 months to 3 years have no localizing signs of infection.[2]

The incidence of invasive pneumococcal disease in children has come down because of polysaccharide vaccine. The increased incidence of bacteremia among young children may be due to part of maturational immune deficiency in the production of opsonic IgG antibodies to the polysaccharide antigens present on encapsulated bacteria.

Fever is a common presenting symptom in paediatric out patient practice and in children less 3 years of age. Approximately 20% to 30% of the children may have no identifiable cause of fever after history and physical examination.[4,5]

Although most of these children will have a benign viral illness, children less than 3 years of age are at increased risk of clinically undetectable serious bacterial infection (SBI). The incidence of serious bacterial infection is roughly about 10-15% of previously healthy children presenting with rectal temperature more than 39^0c. Approximately 2-3% of these children have Occult Bacteremia (OB)[6,7,8]

2-8% have UTI depending on the age and gender.[9]

Other causes of serious bacterial infection include occult bacterial pneumonia[10] in 3% of children less than 3 months, 5% will have other infections such as bone and joint infection, meningitis, soft tissue infection or bacterial enteritis. Although antibiotic treatment is necessary for children with serious bacterial infection it is also important to limit therapy in those children at greatest risk.

Common etiological agents in less than 3 months: Group B Streptococci and Listeria monocytogens, Salmonella, E.coli, Neisseria etc.

Fever is a controlled increase in body temperature over the normal values for an individual. Body temperature is regulated by thermosensitive neurons located in the preoptic or anterior hypothalamus that respond to changes in blood temperature as well as to direct neural connections with cold and warm receptors located in skin and muscle.

Thermoregulatory responses include redirecting blood to or from cutaneous vascular beds, increased or decreased sweating, extra cellular fluid volume regulation (via Arginine vasopressin) and behavioural responses, such as seeking a warmer or cooler environmental

temperature. Normal body temperature also varies in a regular pattern each day. This circadian temperature rhythm, or diurnal variation, results in lower body temperature in early morning and temperatures approximately 1^0C higher in the late afternoon and early evening.

PATHOGENESIS

Fever is regulated in the same manner as normal temperature is maintained in a cool environment, the difference being that the body's thermostat has been reset at a higher temperature.

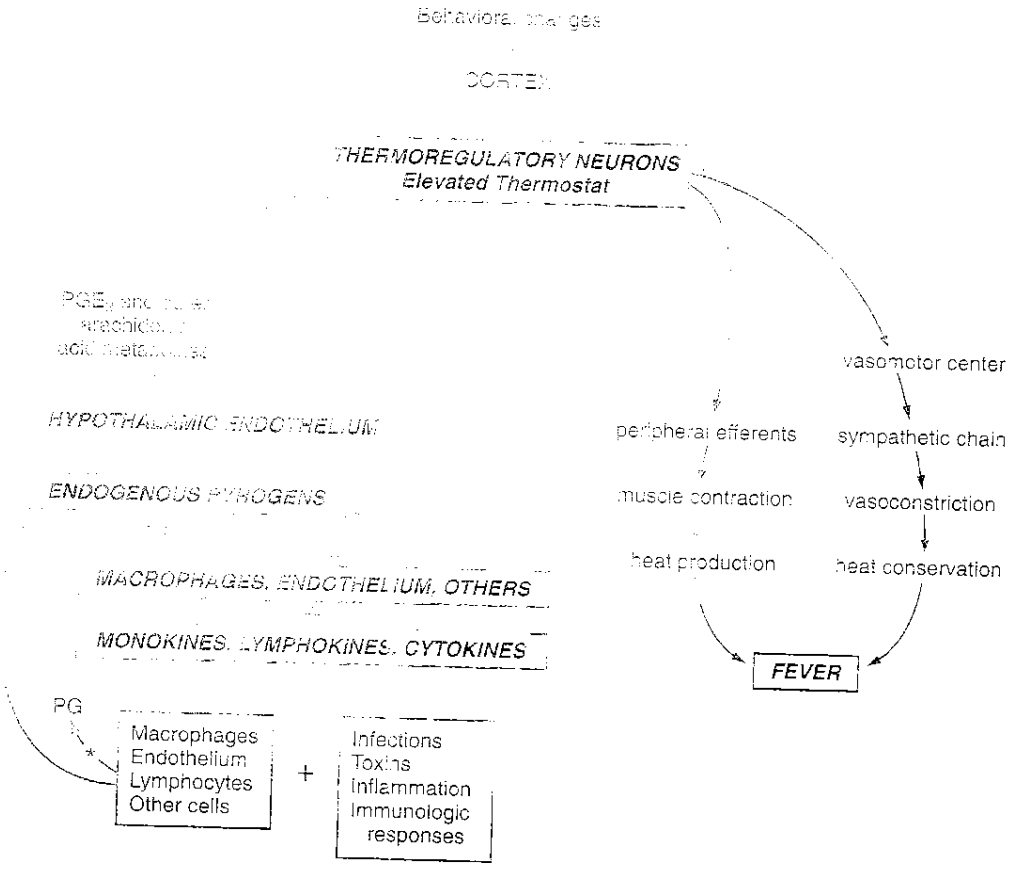
Whatever may be the cause, endogenous pyrogens including the cytokines, interleukin 1, interleukin 6, tumor necrosis factor α, interferon β, interferon γ and other cells produce lipids also serve as endogenous pyrogens.

Most of the endogenous pyrogen molecules are too large to cross blood-brain barrier in an efficient manner. However circum ventricular organs in close proximity to the hypothalamus lack a blood brain barrier and allow for neuronal contact with circulating factors through fenestrated capillaries.

Microbes are most common exogenous pyrogens, which are substances that come from outside the body, stimulate macrophages and other cells to produce endogenous pyrogens, and result in fever.

Fever can be taken as a indicator of infection. Fever may be considered as an early manifestation of sepsis.

Fever is associated with increased oxygen consumption and carbon dioxide production. Increased risk for febrile seizures hence fever should be treated. Intermittent fever with wide fluctuations is characteristic of sepsis.



Axillary temperature more than 37.5^{o}C is uncommon in first two months of life. Fever in young infant may indicate serious bacterial infection and may be the only sign according to integrated management of childhood illnesses.

DIAGNOSIS

By careful history and physical examination subtle signs such as tachycardia, lethargy, irritability may be present for the diagnosis of serious bacterial infections. Clinical observations alone lack necessary sensitivity and specificity in detecting occult bacterial infection.[11]We need some laboratory test to find occult bacteremia.Blood cultutre remains gold standard ,and takes an average time of 24 hours[12]

Total White blood cell count, band count, cultures of blood, urine, cerebrospinal Fluid (CSF) examination may find clue for sepsis. The total white blood cell count is the commonly used screening test for occult bacteremia.

Total White Blood Cell count (WBC) ≥ 15,000 may be taken as determining factor for starting antibiotic therapy[13]. However, because of its low predictive value, empirical treatment based on a WBC ≥ 15,000 results in unnecessary treatment in 85% to 95% of cases.[6,13]

Recent data suggest that the absolute neutrophil count (ANC) is a more accurate test in detecting occult bacteremia[6,8] however the overall profile of absolute neutrophil count is similar to that of White blood cell count.[8] ANC calculated using the formula Segmented neutrophils plus band neutrophils equals total neutrophils multiplied with total WBC count and removing the decimal point gives rise to absolute neutrophil count.[1]

Formula for calculating the ANC

ANC = 10 x WBC Count in 1000's x (Percentage of Polymorpho leucocytes + percentage of Band cells)

Normal Value : More than 1500 cells / mm3.

Mild Neutropenia : More than 1000 – Less than 1500/mm3.

Moderate neutropenia : More than 500 – Less than 1000/mm3.

Severe neutropenia : < 500/mm3.

Blood culture, urine culture and X-ray chest remains gold standard; however, average time for detection of positive cultures is 15 to 16 hours and may be as long as 24 to 48 hours.[7,12] Urinary tract infection (UTI) is the most common cause of occult serious bacterial infection in this age

group, can be predicted and confirmed by culture methods.[9] Colony count more than 1,00,000 (10^5) is confirmatory. It is very difficult to differentiate between bacterial and viral pneumonia based on chest radiograph alone.[10]

Rectal temperature > 39^0C usually presents with common organism in New born and infants between 1 to 3 months:

a) Group B streptococci

b) E. coli K_1

c) Listeria monocytogenes

3 months to 36 months:

a) H. influenza type b

b) S. pneumoniae,

c) N. meningitidis

d) Salmonella

These organisms account for 90% of occult bacteremia. In pre H-influenza B era children with temperature more than 41°C are associated with 9.3% of occult bacteremia. In post H-influenza B era

temperature more than 40.9°C are associated with 2.8% of occult bacteremia.

Risk factors indicating bacteremia are

1. Temperature ≥ 39^0C
2. WBC count > 15000 cells μ/L
3. Elevated ANC more than 10,000 cells μ/L
4. Elevated Erythrocyte sedimentation rate (ESR)
5. CRP >6mg/dl

COMPLICATIONS

Occult bacteremia may resolve spontaneously or may lead to localized infections such as meningitis, pneumonia, cellulitis, pericarditis, osteomyelitis, or suppurative arthritis.

Primary prevention: Immunization with H.influenza B- vaccine 3 doses at 2, 4 ,6 months and booster at 15 months or PRP-OMP (2 doses) at 2,4 months and booster at 12 months. Primary vaccination causes a decline in the incidence of H-influenza B infection.

Three doses of Pneumococcal 7 valent conjugate vaccine PCV 7

are recommended to be given at 2,4,6 months of age and 4th dose at 12-15 months. Meningococcal vaccine also to be given to prevent meningitis.

TREATMENT

Children with temperature more than 39° C should be started on empirical antimicrobial therapy with ceftrioxone 50 mg/kg after obtaining blood culture. If WBC more than 15,000 cells μ/L start antimicrobial therapy.

Clinical observations alone lack necessary sensitivity and specificity in detecting occult bacterial infection.[11]CRP may be helpful in this clinical situation[14,15,16,17,18,19,20]

'C' Reactive Protein (CRP)

C reactive protein was identified by Tilet and Francis in the year 1930.It is isolated from the plasma of patients with pneumonia.It was named because of its ability to bind and precipitate C polysaccharide of pneumococcus. It is synthesized by the liver. Normally it is present in trace amounts in serum .The amount is < 0.3mg/dl .

CRP estimation is simple and rapid test and does not require expertise. It is less expensive and results will be available within short

time.It is an acute phase reactant belonging to a group of serum proteins called “PENTAXTRINS”. It is normally present in trace amounts in blood of healthy individuals. Its level increases within hours of acute injury or onset of inflammation and reaches peak within 24 to 48hours.In serum it is found in association with very low density lipoproteins.CRP is elevated in all bacterial infections in acute stages.

Biochemical properties: It has a molecular weight of approximately 1,10,000 daltons. CRP consists of five apparently identical monovalently bound polypeptide units. Each subunit has a molecular weight of 21,500 daltons and is composed of 189 aminoacid residues with one disulphide bond.

In electron microscopy the sub unit appears spherical and the entire CRP molecule has a shape of pentagon. Studies of the binding specificities have indicated that CRP has reactivity with phophocholine and phosphate esters and hence with lipids widely distributed in mammalian microbial cells and with widely distributed polycations including those derived from leucocyte granules. Interaction with either of these ligands has been shown to alter CRP in such a way, that it can bring about activation of the complement system with generation of all known complement dependant activities including complement

consumption, adherence, phagocytosis and cytolysis.

Experimentally CRP synthesis and production of acute phase reactants have been shown to be induced by a factor released from macrophages. Since this factor has been independently discovered by many investigators it has many names.

- Interleukin I
- Lymphocyte activating factor
- Lymphocyte endogenous mediator
- Endogenous pyrogen

C Reactive Protein is an acute phase reactant. Other acute phase reactants include serum ceruloplasmin, α-1 antitrypsin, haptoglobin, procalcitonin etc.

Measurement of C-reactive protein, an acute phase protein synthesised by hepatocytes is a valuable measure in distinguishing systemic bacterial and viral infection in both immunocompetent and immunodeficient hosts. After the onset of inflammation or acute tissue injury, CRP synthesis increases within 4 to 6 hours, doubling every 8 hours thereafter, peaks by 36 hours after the onset of inflammation. The

kinetics of CRP metabolism seem to closely parallel the degree of injury and repair, there by supporting its value as an acute measure of disease activity. CRP has high positive predictive value, negative predictive value, sensitivity and specificity.

We sought to prospectively study the diagnostic properties of semiquantitative CRP in comparison will other clinical and laboratory predictors of occult SBI.

Bacterial infection may be acute and life threatening. The relationship between acute infectious disease and WBC, absolute neutrophil count (ANC) and band neutrophils has been recognized for many years. ANC is more accurate than total WBC in predicting bacteremia. More than 10,000 cell /cumm indicates sepsis. Bacterial sepsis may be one of the cause for neutropenia less than 1500 cells /cumm.

REVIEW OF LITERATURE

Goh PL, et al from Accident and Emergency Department, Changi General Hospital, Singapore in a study to identify predictors of serious bacterial infection in children aged between 3 to 36 months with fever without source. Screened inpatient records of all children aged 3 to 36 months admitted from the Emergency Department of Singapore's main paediatric hospital between October 2001 to February 2002 with International Classification of Diseases (ninth revision) diagnosis codes 038 (septicaemia), 079 (viral fever), or 780 (pyrexia of unknown origin). Patients identified as having fever without source were enrolled.

Of 86 enrolled children, 17 (19.8 percent) had serious bacterial infection. Duration of fever and white blood cell count were found to be significant predictors. Children with white blood cell count equal to or greater than 16,000/cubic mm had 6.9 times (95 percent confidence interval [CI] is 1.7 to 28.4) increased risk of serious bacterial infection, while children with fever of duration exceeding three days before presentation had 3.8 times (95 percent CI is 1.1 to 13.1) increased risk of serious bacterial infection.

The authors concluded that the two identified predictors offer an estimate of the risk of serious bacterial infection in children aged 3 to 36

months with fever without source.

Pratt A, et. al. Department of Pediatrics, Division of Emergency Medicine, Robert Wood Johnson University Hospital, New Brunswick, New Jersey, USA to assess WBC, ANC and CRP values as predictors of SBI in relation to duration of fever, patients who presented to a pediatric emergency department between the ages of 1 and 36 months, with fever ≥ 39^0 C and no source of infection had a complete blood count (CBC), blood culture, and CRP levels drawn. A urinalysis and/or urine culture was obtained when age and gender appropriate. A chest radiograph was performed at the discretion of the treating physician. The study subjects were enrolled prospectively and then divided into two groups based on duration of fever of ≤ 12 hours or >12hours and were compared.

One hundred and twenty-eight patients were originally enrolled. Nine patients were excluded. Seventeen patients (14%) had SBI. One patient (<1%) had bacteremia, three (3%) had pneumonia and 13 (10%) had urinary tract infections.

Forty-five patients presented with fever ≤12 hours and 74 patients presented with fever >12 hours. Area under the curve (AUC) for WBC, ANC and CRP was significantly larger in patients with SBI presenting with fever >12 hours (0.85, 0.83, 0.92 respectively) compared to patients

with SBI who presented with fever for <12 hours (0.37, 0.42, 0.68 respectively).

Conclusion drawn by the authors is that bacterial markers studied were more predictive of SBI if the duration of fever was >12 hours. CRP performed was better than WBC and ANC in both scenarios.

Isaacman DJ, et.al. from department paediatrics Children's Hospital of The King's Daughters, Norfolk, USA in a study to assess the utility of serum C-reactive protein (CRP) as a screen for occult bacterial infection in children, febrile children aged 3 to 36 months who visited an urban children's hospital emergency department and received a complete blood cell count and blood culture as part of their evaluation were prospectively enrolled from February 2, 2000, through May 30, 2001. Informed consent was obtained for the withdrawal of an additional 1-mL aliquot of blood for use in CRP evaluation. Logistic regression and receiver operator characteristic (ROC) curves were modeled for each predictor to identify optimal test values, and were compared using likelihood ratio tests. Two hundred fifty-six patients were included in the analysis, with a median age of 15.3 months (range, 3.1-35.2 months) and median temperature at triage 40^0 C (range, 39.0^0C-41.3^0C). Twenty-nine (11.3%) cases of occult bacterial infection (OBI) were identified, including 17 cases of

pneumonia, 9 cases of urinary tract infection, and 3 cases of bacteremia. The median white blood cell count in this data set was 12.9 x 10(3)/µ L [corrected] (range,3.6-39.1 $x10^3/\mu L$) [corrected], the median absolute neutrophil count (ANC) was 7.12 x 10^3/L [corrected] (range, 0.56-28.16 $x10^3$/L) [corrected], and the median CRP level was 1.7 mg/dL (range, 0.2-43.3 mg/dL). The optimal cut-off point for CRP in this data set (4.4 mg/dL) achieved a sensitivity of 63% and a specificity of 81% for detection of OBI in this population. Comparing models using cut-off values from individual laboratory predictors (ANC, white blood cell count and CRP) that maximized sensitivity and specificity revealed that a model using an ANC of 10.6 $x10^3$/L [corrected] (sensitivity 69%; specificity 79%) was the best predictive model. Adding CRP to the model insignificantly increased sensitivity to 79%, while significantly decreasing specificity to 50%. Active monitoring of emergency department blood cultures drawn during the study period from children between 3 and 36 months of age showed an overall bacteremia rate of 1.1% during this period. CONCLUSIONS: An ANC cut-off point of 10.6 $x10^3$/L [corrected] offers the best predictive model for detection of occult bacterial infection using a single test. The addition of CRP to ANC adds little diagnostic utility. Furthermore, the lowered incidence of occult bacteremia in our population supports a decrease in the use of diagnostic

screening in this population.

Shaoul R, et. al from Israel studied the value of CRP compared to total leukocytes (WBC) and absolute neutrophil count (ANC) in differentiating positive, contaminated and negative blood cultures in various pediatric infectious diseases (pneumonia, acute gastroenteritis (AGE), urinary tract infection (UTI) and acute otitis media (AOM)). Data was collected retrospectively from patients who were admitted to or discharged from the pediatric ward with one of the above diagnoses. Children with chronic diseases or with immunodeficiency were excluded from the study. CRP levels were significantly higher in the positive culture group versus contaminated and negative groups (101 mg/L, 30.9 mg/L, 34.3 mg/L, respectively). The total leukocytes and ANC were not of value. When divided into diagnostic subgroups, CRP levels were significantly higher in the positive blood culture groups in patients with pneumonia and AGE. The sensitivity of a CRP value above 85 mg/L for pneumonia and UTI and above 30 mg/L for AGE and AOM in discriminating true positive versus contaminated culture was 70% with a specificity of 67.6% and positive predictive value of 60.3%. Conclusions: CRP may be used for differentiation between positive and contaminated blood cultures in children and have been shown to be a better predictor than WBC or ANC for this purpose.

Hsiao AL, et.al from Yale University School of Medicine, USA conducted a prospective study of febrile infants aged 57-180 days old. Evaluation included blood and urine tests and direct fluorescent antibody (DFA) of nasal swabs for respiratory viruses. Additional studies were performed at the discretion of managing clinicians. Serious bacterial illness (381) was diagnosed in 44 (10.3%) of 429 infants: 41 with bacteruria and 4 with bacteremia (1 infant had concurrent Escherichia coli bacteruria and bacteremia). Lumbar puncture, performed in 58 (13,5%) infants, revealed no cases of bacterial meningitis. DFAs were positive in 163 (38.0%) infants, the majority were respiratory syncytial virus or influenza A. SBI was noted in 4.9% of infants with positive DFA. Age and height of fever were not significant predictors of SBI. White blood cell count (17.1 K/mm^3 vs 12.4 K/mm^3) and CRP (2.6 mg/dL vs 0.9 mg/dL) were elevated in infants with SBI, as was the Yale Observation Score (9.4 vs 3.0). Authors concluded that a substantial proportion (10.3%) of older febrile infants have SBI. In the postpneumococcal vaccine era, only 1 infant had pneumococcal disease; bacteremia was noted in 0.9%. Bacteruria is commonly associated with fever in this age range. Infants older than 8 weeks remain at risk for Bacteremia and bacteruria, regardless of positive DFA or other apparent source of fever, CRP is a better indicator than white blood cell count, but no single ideal

indicator of SBI was identified for this age group.

Andreola B, et.al from Italy to assess the value of procalcitonin (PCT) and C-reactive protein (CRP), compared with that of total white-blood cell count (WBC) and absolute neutrophil count (ANC), in predicting severe bacterial infections (SBIs) in febrile children admitted to Emergency Department. METHODS: A prospective study was conducted in 408 children aged 7days to 36months, admitted with fever without source, at a tertiary care Pediatric Emergency Department. PCT, CRP, WBC, and ANC were determined upon admission and compared. Specificity, sensitivity, multilevel likelihood ratios, receiver operating characteristic (ROC) analysis, and multivariate stepwise logistic regression were carried out. SBI was diagnosed in 94 children (23.1%). PCT, CRP, WBC, and ANC were significantly higher in this group than in non-SBI patients. The area under the ROC (AUC) obtained was 0.82 (95% CI: 0.78-0.86) for PCT, 0.85 (95% CI: 0.81-0.88) for CRP (P = 0.358), 0.71 (95% CI: 0.66-0.75) for WBC, 0.74 (95% CI: 0.70-0.78) for ANC. Only PCT (OR: 1.32; 95% CI: 1.11-1.57; P < 0.001) and CRP (OR: 1.02; 95% CI: 1.01-1.03; P < 0.001) were retained as significant predictors of SBI in a multiple regression model. For infants with fever <8 hours (n = 45), AUC for PCT and CRP were 0.92 (95% CI: 0.80-0.98) and 0.75 (95% CI: 0.60-0.87), respectively (P = 0.056). The conclusion at

the end of the study was that both PCT and CRP are valuable markers in predicting SBI in children with fever without source and they perform better than WBC and ANC. PCT appears more accurate at the beginning of infections, but overall CRP may be the most convenient marker for its better sensitivity and feasibility.

Gajdos V, et.al from France studied to identify predictive factors of the presence of a serious bacterial infection (SBI) in febrile infants less than three months old did a retrospective analysis of the medical files of 315 consecutive consultations of febrile infants less than three months old in the pediatric emergency department of a French hospital, with logistic regression multivariate analysis of the different criteria routinely considered and C-reactive protein (CRP). SBI were diagnosed in 79 (25.1%) infants, primarily urinary tract infections (71; 22.5%). One of these 79 children had pneumococcal meningitis but met the classical criteria for low risk of SBI, he died because antibiotics were not prescribed sufficiently early. Factors significantly associated with SBI were: male sex; temperature >38.5^0 C and lasting >24 hours; poor general condition; absence of ear, nose and throat symptoms; high white blood cell count with >50% neutrophils; and serum CRP concentration >20 mg/ 1. Multivariate analysis entering all these items retained only the latter two (respectively, OR: 13.5, 95% CI: [6.5-28.2] and OR: 2.9; 95% CI:

[1.3-6.3]) CRP <20 mg/1 and <50% neutrophils- had a negative predictive value of 93.1% for the absence of SBI.

Rasamoelisoa JM, et.al from Madagascar carried out retrospective study at the pediatric service of the General hospital of Befelatanana in Antananarivo for 48 months (1997-1998). The population of this study was continued of 361 patients taken from 714 febrish children. 384 CRP were performed. The initial CRP measurement allowed to differentiate 152 presumed bacterial infections: 49 respiratory tract infections, 62 in neurological pathology, 10 in digestive pathology, 19 in otorhinolaryngology pathology, 12 in urinary pathology and 153 presumed viral infections: 86 respiratory tract infections, 29 in neurological pathology, 12 in digestive pathology, 26 in otorhinolaryngology pathology. There was a right correlation of CRP values and leukocyte levels in presumed bacterial infections. Specificity and sensibility of the test applied in different child febrish diseases were satisfactory. CRP measurement is easy and rapid to perform. It is useful and seems to be the appropriate method to diagnose childhood febrish diseases in countries where facilities are insufficient and financial possibilities limited.

Marcus, N. et.al, unit of emergency Medicine from Israel in a

study investigated the validity and feasibility of the 2 minute bed side quick read test in the prediction of bacterial pneumonia in children in the emergency department. Fifty children selected from 4 days to 17 years randomly selected with symptoms and signs of pneumonia over a 6 month period, were prospectively studied. The diagnosis of bacterial and viral pneumonia was based on clinical and radiological findings. CRP measured using a QR-CRP kit. 36 persons (72%) were diagnosed with bacterial pneumonia and 14% with viral pneumonia mean CRP levels 26mg/L P (0.007) significantly higher CRP levels were associated with bacterial than with viral pneumonia. He concluded that QR-CRP seems to be a useful predictor of bacterial pneumonia in children especially those with illness of shorter duration and is feasible for use in the emergency department.

Bleeker S.E, et.al from department of paediatrics, Sophia children's hospital, Netherlands conducted a study to design a clinical rule to predict the presence of serious bacterial infection in children with fever without apparent source. Information was collected from the records of children aged 1-36 months who attended the emergency department with fever more than 38^{o}C without apparent source. After evaluation twenty five percent of the 231 patients enrolled in the study had serious bacterial infection. The independent predictors from laboratory tests were white blood count, serum C-reactive protein and the presence of more than 70

white blood cells in urine analysis. The Author concluded that the probability of serious bacterial infection in a individual patient with fever without source can be estimated more precisely by using a limited number of symptoms, sign and laboratory tests.

Pulliam P.N., et. al, in department of paediatrics, Philadelphia, USA in a study to determine the diagnostic properties of quantitative CRP associated with clinically undetectable serious bacterial infection in febrile children aged 1 to 36 months. Febrile children presenting to the emergency department with temperature more than 39^{o}C without source were enrolled. In this prospective cohort study emergency department temperature, duration of fever and clinical evaluation using the Yale observation scale were recorded at the time of the initial evaluation, white blood cell count, band count, absolute neutrophil count, CRP were measured at the same time. All patients received blood culture, urine analysis, urine culture, and chest radiograph. The cutoff point of 7 was determined to maximize the sensitivity 79% and specificity 91% and likelihood ratio of 8.3. The conclusion of the study was quantitative CRP is a valuable test in the evaluation of febrile young children who are at risk for occult bacteremia and SBI, with a better predictive value more than WBC or ANC.

Putto, A, et.al studied prospectively 154 febrile children to determine the diagnostic value of the quantitative serum C reactive protein concentrations in children with acute otitis media, acute

tonsillitis, or treated with antibiotics during the two previous weeks and infants less than 2 months of age were excluded. Ninety seven children were from private paediatric practice and 57 were patients who had been admitted in hospital. The comparison group consisted of 75 children with confirmed bacterial infections whose CRP value were recorded prospectively. In the study group 23% children had a confirmed viral infection, 59% had a probable viral infection as judged from outcome of illness, 18% had a bacterial or probable bacterial infection when the duration of the disease was more than 12 hours and the CRP value less than 28 mg/L. In addition CRP value greater than or equal to 40 mg/L detected 79% of bacterial infections, with 90% specificity. The data show that determination of CRP concentration is a valuable tool in evaluating children who have been ill for more than 12 hours.

Galetto – Lacour A et.al from Geneva, conducted a prospective study of population 99 children aged 7 days to 36 months with fever more than 38^{o}C with no localizing sign of infection at the emergency department. Blood procalcitonin, C-reactive protein, and interleukin 6 values were determined using rapid tests and were compared with the WBC and differential count clinical score. 29% children received a diagnosis of having an SBI. PCT had the best sensitivity (93%) and negative predictive value 96%. PCT less than 0.5 ng/L rules out SBI, more than 2 ng/L increased probability of SBI to 68%. CRP less 40mg/L generated posttest probability for SBI of 9.7% more than 100 mg/L generated posttest probability increased to 86.5%. The study concluded

that PCT and CRP performed were better than IL-6/ WBC, band count in predicting the occurrence of SBI. PCT and CRP bed side tests maybe useful tools for emergency and private practice doctors and should be considered in the initial workup of children with fever with out source.

Lohen R, et.al, in hospital from France, a study was undertaken to evaluate correlation between two technique of CRP, one by usual laboratory technique and other by a rapid test, and to evaluate the impact of this rapid test for febrile children at the emergency room. 572 children were included, comparison of two methods showed 93% a fairly good linear correlation. Duration of children management in the units was approximately two times shorter when rapid CRP test was used. The study concluded that rapid CRP test is better than routine CRP test for febrile children in the emergency units

STUDY JUSTIFICATION

- 1 – 36 months children are more prone for serious bacterial infection. Among febrile children few of them will have serious bacterial infection.

- In order to differentiate between children with or without occult bacteremia and serious bacterial infection CRP is a useful test with high sensitivity, specificity, PPV & NPV.

- Febrile children without a clinically identifiable focus pose a great difficulty in decision making to give antibiotics or not.

- If we don't give antibiotics, child may land up in serious bacterial infections, if we give antibiotics it may lead to a increase in cost factor, time factor, parenteral anxiety, antibiotic resistance and alteration of the normal flora.

- To differentiate between those with serious bacterial infection and those without serious bacterial infection CRP concentration is a superior test than total WBC.

- Few Indian studies are available on the role of CRP in diagnosing meningitis.

- CRP may be used as a tool for sepsis screening in newborn.

- Not much Indian studies are available for estimation of CRP in febrile children aged 1-36 months with clinically undetectable serious bacterial infection.

OBJECTIVES

To evaluate

a) The diagnostic value of C - reactive protein (CRP) by semiquantitative method in predicting occult serious bacterial infection in febrile children between 1-36 months of age.

b) Compare it with other diagnostic tests like WBC, ANC and ESR.

c) Various combinations of these tests in predicting occult serious bacterial infection among children between 1-36 months of age hospitalized in an urban referral centre

SUBJECTS AND METHODS

METHODOLOGY

Study Design : Descriptive Study Evaluation of A Diagnostic Test

Study Place : Institute of Child Health and Hospital for Children, Egmore, Chennai. Outpatient and Inpatient Departments/Wards.

Study Period : October 2007 to September 2008

Study Population :1-36 months

Inclusion Criteria

a) Children aged 1-36 months

b) Fever more than 12 hours up to 7 days [1]

c) Without obvious focus of infection on clinical examination.

Sample Size : 140 as per statistician.

Exclusion Criteria

a) Children who have received prior antibiotics and vaccines.

b) Children with underlying immunological disease.

MANOEUVRE

Children in the age group of 1-36 months presenting to the outpatient department and in various wards of Institute of Child Health and Hospital for Children, Egmore, Chennai in the period between October 2007 to September 2008 were screened for temperature >39°C and who satisfied inclusion criteria were included in the study. Temperatures were recorded either in the axillary or rectal areas. Informed consent was obtained from parents or guardian & clearance of Institutional Ethical Committee Review Board. Blood samples were taken for total WBC count, ANC, ESR and CRP and at the same time samples for blood culture. Blood cultured in various media incubated overnight and colony morphology was read. Urine analysis, urine culture, colony count, chest radiograph were done. CSF analysis was done for selected cases. Patients were reviewed thereafter. CRP was done by slide agglutination method. Qualitative CRP followed by Semiquantitative CRP was performed. CRP-Agglutination in highest serum dilution corresponds to amount of CRP in mg/dl. The findings were recorded in a prescribed data entry form.(Annexure).

CRP Estimation: It is based on the principle of agglutination. One drop of test specimen is placed on a slide after centrifugation using a disposable pipette to which a drop of CRP reagent is added. Both test specimen and the reagent to be uniformly mixed over the entire circle,

using a mixing stick. The slide is gently rocked to and fro and considered Negative if no agglutination occurs, if positive CRP concentration is more than 0.6 mg /dL.Dilution and semiquantiative test was done for all cases. S x D = mg/dl =Quantitative CRP was calculated for all cases.

RESULTS

Total numbers of children studied were: 140.

Children with serious bacterial infection: 30

Children without serious bacterial infection: 110

140 children aged 1-36 months were enrolled in the study. All children under went thorough clinical examination. They were all subjected to screening tests like CRP, Total White Blood Cell count, ESR, Absolute neutrophil count and other investigations as appropriate. These children were divided into SBI and no SBI. The results were tabulated and analyzed using simple statistical proportions. Sensitivity, Specificity, Positive predictive value and Negative predictive value for all tests were compared with gold standards.

Table1:Various diagnostic tests among children with or without SBI

Test	SBI		
	Positive	**Negative**	
WBC≥15000	9	13	22
<15000	21	97	118
Total	30	110	140

WBC ≥15000 was observed in 9 cases of children who had SBI giving rise to sensitivity of 30%,97 children who did not have SBI have WBC <15000 giving a specificity of 88% .Among 22cases with WBC more than 15000 only 9 (40.9%) cases had SBI giving PPV of 41%.Among 118 cases of WBC <15000 97(82.2%) cases did not have SBI giving a NPV of 82%.

Table 2

Test	SBI		Total
	Positive		
ESR≥15mm	16	16	32
<15mm	14	94	108
Total	30	110	140

ESR ≥ 15mm was observed in16 cases of children who had SBI giving rise to sensitivity of 53%, 94 children who did not have SBI have ESR<15mm giving a specificity of 85%. Among 32cases ESR more than 15mm only 16 (50%) cases had SBI giving PPV of 50%.Among 108 cases 94 (87%) of cases ESR<15mm did not have SBI giving a NPV of 87% .

Table 3

Test	SBI		Total
	Positive		
ANC≥10000	9	6	15
<10000	21	104	125
Total	30	110	140

ANC ≥10000 was observed in 9 cases of children who had SBI giving rise to sensitivity of 30%, 104 children who did not have SBI have ANC <10000 giving a specificity of 95%. Among 15cases ANC more than 10000 only 9 (60%) cases had SBI giving PPV of 60%.Among 125 cases of ANC <10000 104(83%) cases did not have SBI giving a NPV of 83% .

Table 4

Test	SBI		Total
	Positive		
CRP≥6mg/dl	23	7	30
<6mg/dl	7	103	110
Total	30	110	140

CRP≥6mg/dl was observed in 23 cases of children who had SBI giving rise to sensitivity of 77%, 103 children who did not have SBI have CRP<6mg/dl giving a specificity of 94%. Among 30cases with CRP more than 6mg/dl only 23 (76.7%)cases had SBI giving PPV of 77%.Among 110 cases of CRP <6mg/dl 103(93.6%) cases did not have SBI giving a NPV of 82%.

Table 5: Predictors of SBI

	Sensitivity (95% C.I.)	**Specificity (95% C.I.)**	**PPV (95% C.I.)**	**NPV (95% C.I.)**	**Likelihood Ratio (95% C.I.)**
WBC	30 (14.6 , 46.4)	88 (82.2 , 94.2)	41 (20.4 , 61.5)	82 (75.3 , 89.1)	2.5 (1.2 , 5.4)
ESR	53 (4.2 , 35.5)	85 (3.0 , 78.9)	50 (3.3 , 67.3)	87 (80.7 , 93.4)	3.7 (2.1 , 6.4)
ANC	30	95	60	83	5.5

	(13.6 , 46.4)	(90.3 , 98.8)	(35.2 , 84.8)	(76.7 , 89.8)	(2.1 , 14.0)
CRP	77 (61.5 , 91.8)	94 (89.1 , 98.2)	77 (61.5 , 91.8)	94 (89.1 , 98.2)	12.0 (5.7 , 25.0)
CRP &WBC	57 (31.2 , 83.1)	99 (96.8 , 100.0)	89 (68.4 , 100.0)	94 (89.0 , 98.6)	52.6 (7.1 , 389)
CRP&ANC	57 (31.2 , 83.1)	100 (100.0 , 100.0)	100 (100.0 , 100.0)	94 (89.7 , 98.7)	-
WBC&ANC	30 (13.6 , 46.4)	94 (89.7 , 98.7)	60 (35.2 , 84.8)	82 (75.3 , 89.1)	5.2 (2.0 , 13.3)
CRP&WBC &ANC	57 (31.2 , 83.1)	100 (100.0 , 100.0)	100 (100.0 , 100.0)	94 (89.0 , 98.6)	-

- Using CRP and WBC combination when compared to WBC alone as a predictive test, sensitivity increased to 57%, specificity increased to 99%, PPV increased to 89% and NPV increased to 94%.

- CRP and ANC combination when used than isolated ANC for predicting SBI sensitivity is increased to 57%but little less than isolated CRP. Specificity increased to 100%, PPV increased to 100% and NPV increased to 94%.

- WBC and ANC combination when used the sensitivity, specificity,

PPV, NPV remained to be the same.

- When CRP&WBC&ANC combination was used sensitivity remained to be same as that of CRP and WBC, CRP and ANC .The specificity increased to 100%, PPV increased to 100% and NPV increased to 94%.

Table 6(i) Comparison of characteristics of CRP Positive and Negative

Duration of fever	**Total**	**CRP**		**P value**
		Positive n (%)	**Negative n (%)**	**0.7**
≤ 24 hours	9	1(11.1)	8(88.9)	
24-72 hours	111	24(21.6)	87(78.4)	
≥72hours	20	5(25)	15(75)	

When fever was more 24 hours duration CRP was positive in 29(21%) cases when compared to 102 cases(73%) across CRP negative. However duration of fever is insignificant. p value is 0.7

Table 6(ii)

S.No.	Age in months		CRP		P value
			Positive n (%)	Negative n (%)	0.10
1.	1-12	50	12(24)	38(76)	
2.	13-24	59	8(13.6)	51(86.4)	
3.	25-36	31	10(32.3)	21(67.7)	

Among age more than 12 months 18 (20%) cases were CRP positive, when compared to 72 (80%) across CRP negative. p value is insignificant. (0.1)

Receiver operating characteristic curve(ROC)

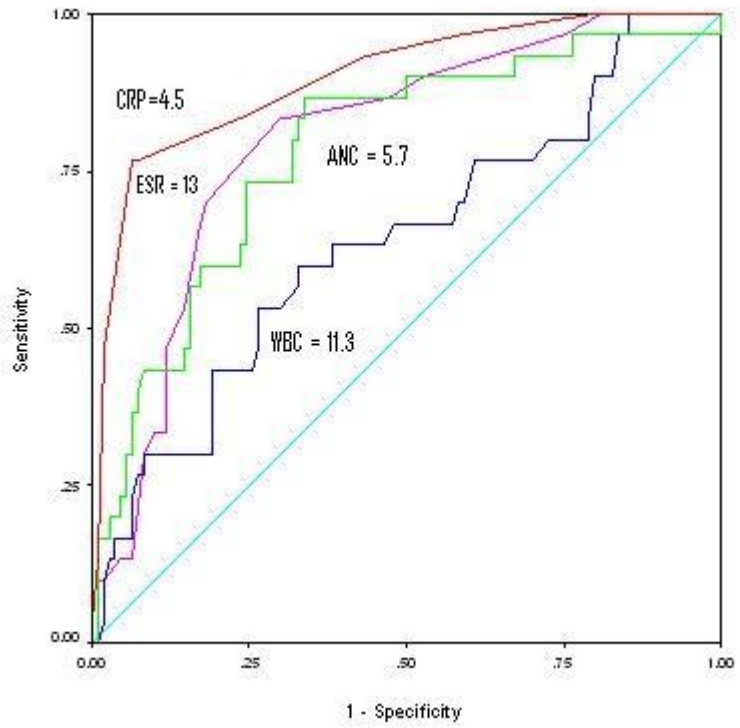


Fig. ROC for variables associated with SBI. Area under the curve for CRP 0.898 (95% CI: 0.832, 0.965); for ESR 0.801 (95% CI: 0.523, 0.755); for ANC 0.783 (95% CI: 0.688, 0.879); and for WBC 0.639 (95% CI: 0.523, 0.755)

Table 7 Predictors of SBI (based on ROC curve)

	Cut off *Point*	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Likelihood Ratio (95% C.I.)	PPV (95% C.I.)	NPV (95% C.I.)
WBC	11.3	60.0 (42.6 , 75.6)	61.8 (57.1 , 66.1)	1.6 (1.1 , 2.3)	30.0 (21.3 , 37.8)	85.0 (78.5 , 90.8)
ESR	13.0	70.0 (53.2 , 83.3)	81.8 (77.2 , 85.5)	3.9 (2.4 , 6.1)	51.2 (38.9 , 61.0)	90.9 (85.5 , 95.0)
ANC	5.7	73.3 (56.2 , 86.3)	73.6 (69.0 , 77.2)	2.8 (1.9 , 4.1)	43.1 (33.0 , 50.8)	91.0 (85.2 , 95.4)
CRP	4.5	83.3 (66.9 , 93.4)	76.4 (71.9 , 79.1)	3.5 (2.4 , 5.1)	49.0 (39.3 , 55.0)	94.4 (88.8 , 97.8)

Based on the ROC curve, cutoff point is fixed for each variable. For WBC the cutoff is 11.3 thousands per cumm. At this cutoff point sensitivity increased to two fold (60%). The cutoff point for ANC is 5.7 thousands per cumm. The sensitivity goes up by two and a half fold. Cutoff point for ESR is 13mm and CRP is 4.5mg /dl. The cutoffs for each variable, along with p value, Sensitivity, Specificity, PPV, NPV, Likelihood ratio are shown in the table7.

Table 8: Multilevel Likelihood Ratios for CRP Concentration

CRP concentration	**SBI**	**No SBI**	Likelihood Ratio **(95% C.I.)**	**Post test probability of SBI**
>15	4	1	14.67 (1.7, 126.4)	80.0
10 - 15	10	3	12.22 (3.59, 41.63)	76.9
6 – 10	9	5	6.6 (2.39, 18.23)	64.3
<6	7	101	0.25 (0.13, 0.49)	6.4
	30	**110**		

To further explore the diagnostic utility of CRP concentration, multilevel likelihood ratios were calculated for a range of CRP concentration shown in table 8.A CRP concentration of ≤ 5mg/dl had a likelihood ratio of SBI of 0.25 corresponding to a NPV of 94%. A CRP concentration of > 15 mg/dl had a likelihood ratio of SBI 14.6, corresponding to PPV of 80%

Statistical analysis

Patients with and without SBI were compared using the 2-tailed t test or Mann-Whitney U test or variables expressed as mean values according to their parametric distribution. χ^2 analysis was used to access the association between variables expressed as percentages and SBI. The variables that gave the best fit was included in the final mode. ROC curve was done to determine the best cut off point for predictor of SBI. The cut-off was obtained from the value that maximized the sensitivity and specificity. For each variable, patients were dichotomized into 2 groups based on the cutoff value. Sensitivity, specificity, likelihood ratio, positive predictive value and negative predictive value of each of the predictors of SBI were determined at the cut off points. Multilevel likelihood ratios for CRP were determined. Statistical analyses were performed using the SPSS statistical software package, version 11.0 for Windows (SPSS, Inc, Chicago, IL). Statistical significance was determined at 5%.

DISCUSSION

The management of febrile young children without apparent source of infection remains controversial, we need a test with adequate sensitivity and specificity to distinguish what type of children are at risk for bacterial infection. Occult bacteremia, urinary tract infection and pneumonia are considered as serious bacterial infection in children(SBI).

Because majority of febrile young children do not have SBI, laboratory tests and expectant antibiotic therapy of these children adds to cost, time, discomfort, parental anxiety and may contribute to antibiotic resistance.

Recent prospective studies of febrile young children have found CRP to be a more sensitive and specific predictor of serious bacterial infection compared to WBC counts[21].

C reactive protein is a classic acute phase reactant. It is a serum protein which is synthesized in the liver . CRP levels are increased in the serum as a result of infection and inflammation. CRP estimation is a rapid diagnostic test. As CRP is easily available, less expensive, less time consuming and a better laboratory test in delineating children with and without SBI[24,25,26,27] , this study was conducted. The diagnostic utility of semiquantitative CRP is evaluated in this study.

140 cases were included in the study. Out of 140 cases 30 cases

were CRP positive, among them 23cases of SBI were identified. 9 cases were occult bacteremia (both CRP and blood culture positive). 4 cases of S.Pneumoniae, 4 cases of H.influenzae and 1 case of Klebsiella were isolated. 6 cases of urinary tract infection were identified (both CRP and urine culture positive) 1 case of klebsiella, 4 cases of E.coli,1 case of H.influenzae were found in this study. 11 cases were diagnosed as pneumonia (both CRP and chest x ray positive).The incidence of occult bacteremia found in this study is 16% .

	CRP	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Likelihood Ratio**
Present study		77%	94%	77%	94%	12.0
Issacman et al		63%	81%	_	_	3.3%
Pullium et al		79%	91%	_	_	8.3%
Shaoul R et al		70%	67.6%	60.3%	_	_

CRP has been evaluated as predictors of bacterial illness in febrile children. CRP was found to be having a sensitivity of 77 %, specificity of 94% PPV of 77%, NPV of 94% and likelihood ratio of 12% in the present study.

The sensitivity of the present study correlates with Issacman and Pullium study but specificity is slightly higher than the Issacman study. In pullium study only 77 children were included, the sample size was small. In Issacman study sample size is higher than the present study. Probably the sample size would have altered the sensitivity. The likelihood ratio is also increased when compared to other studies. CRP was found to be a useful screening test for occult bacterial infection.

Total WBC is the most commonly used laboratory test used in this clinical situation. It is one of the screening test for occult bacteremia.In the present study WBC has a sensitivity of 30% and specificity of 88% .Although the total WBC is less sensitive and specific, because of the low incidence of occult bacteremia, the test has a negative predictive value (NPV) 82% , positive predictive value (PPV) of 44% and likelyhood ratio 2.5% In this study 13 children with WBC more than or equal to 15,000 did not have occult bacteremia. Using a level of more than or equal to 15,000 did not significantly differentiate between children with SBI and Non SBI.

ANC is another test done for predicting bacterial illness[28,28,30,31.] Using ANC as a screening test it has a sensitivity of 30% and specificity of 90%, NPV of 83%,PPV of 60% and likelihood ratio of 8.5%. Based

on our observation it is slightly better than Total WBC. Recent studies concluded that ANC is a better test for detecting pneumococcal bacteremia than WBC, with a approximate cutoff value of 10^9 cells/L.[22,25]

Erythrocyte sedimentation rate has been evaluated as predictors of bacterial illness in febrile children. Our observation was that it has a sensitivity of 53 %, specificity of 85%, NPV of 87%, PPV of 50% and likelihood ratio of 3.7%. Based on this results we consider ESR is better than WBC.

When CRP &WBC combination is used as a predictive test sensitivity increases from 30% to 57%, specificity increases from 88% to 99%,Positive predictive value increased to 89%,Negative predictive value increased to 94%and likelihood ratio of 52.6% when compared to WBC alone.When CRP &ANC combination is used as predictive test sensitivity increases from 30% to 57%,increases specificity from 95% to 100%,increases Positive predictive value from 60% to 100%,increases Negative predictive value from 85% to 94%when compared to ANC alone as predictive test .WBC and ANC combination is found to have increased specificity however, combination of tests is more useful than isolated test except for CRP alone.

As Screening test CRP and ANC combination is better than

isolated ANC and as a specific test CRP & WBC&ANC combination is more useful.

Receiver operating characteristic curves (ROC) for CRP, ESR, ANC, WBC were constructed. Based on the curve, cutoff values for each variable was determined that simultaneously maximizes the sensitivity and specificity. For each variable, patients were dichotomized into 2 groups based on the cutoff value and χ^2 analysis was done to assess the association between the dichotomized variables and the presence of SBI. Multilevel likelihood ratios and CRP concentration were calculated. Cutoff value fixed at 4.5mg for CRP, sensitivity increases from 77% to 83%. For WBC cutoff fixed at 11.3 cells per cumm, which increases sensitivity from 30 % to 60%. ANC has a cutoff point fixed at 5.7 cells/cumm which increases sensitivity from 30% to73.3%. ESR has a cutoff point 13mm which increases sensitivity from 5 3% to 70%.

> Multilevel likelihood ratios and CRP concentration were calculated. A CRP concentration of ≤ 5mg/dl had a likelihood ratio of SBI of 0.25 corresponding to a NPV of 94%. A CRP concentration of > 15 mg/dl had a likelihood ratio of SBI 14.6, corresponding to PPV of 80%. Likelihood Ratios are a powerful clinical tool because a clinician may estimate the pretest probability of the presence of disease in a particular patients.

This study demonstrates CRP is both more sensitive and specific in distinguishing children with occult serious bacterial infection from those without bacterial illness. Based on the curve CRP concentration of more than 4.5mg% that maximizes the sensitivity. A CRP concentration more

than 6mg/dl is helpful rather than total WBC of more than or equal to 15,000.[2,3,35,36,37]

CRP concentration is dependent on the duration of fever [35], suggesting that CRP is more reliable as an indicator of bacterial infection if fever has been present for more than 24hours[19,21,38].However significant number of cases were also negative for CRP in this study.

CRP is one of the early marker for sepsis[32,38]. S. Pneumonia is now the predominant cause of occult bacteremia.[4,7] The use of conjugate pneumococcal vaccine decreases the risk of occult bacteremia. However, the vaccine is only 90% effective in preventing invasive disease, therefore, even vaccinated children will be at risk of invasive pneumococcal disease.[26] For H.influenzae effective vaccine is also available. But it comes under optional vaccine list, in countries like India still many children remain unvaccinated with optional vaccines.

In the clinical setting of febrile young child with no apparent source of fever, the child is at risk for serious bacterial infection in addition to invasive pneumococcal disease.[23] there will remain a need for a rapid screening test for serious bacterial infection even after the use of conjugate pneumococcal vaccine and HiB vaccine.

A limitation to my study is Semiquantitative method of assessment of CRP rather than direct quantitative method. The mean age of children in my sample population was 18 months which is comparatively higher than that of children in other studies this may also affect my prevalence rate.

Both PPV and NPV of a diagnostic test are affected by the prevalence. Higher prevalence of occult serious bacterial infection improves the PPV of a screening test. In this study, I chose CRP for predicting children with occult serious bacterial infection because when a febrile young child with no identifiable source of fever presents the clinician is faced with the dilemma for workup and antibiotic therapy. The most useful test would predict children at risk of bacterial infection and therefore need workup and possible antibiotic therapy.[2,3]

Urinary tract infection remains common occult bacterial infection confirmed by culture and colony count. The results of urine culture are delayed by 24 to 48 hours. Similarly, the diagnosis of occult bacteremia by blood culture is delayed by a mean of 15 to 16 hours and up to 48 hours[12]. Blood culture are positive in 3 to 5% of febrile young children with pneumonia. Children who received a chest radiograph, true prevalence remains unclear.[10] More over it is very difficult to differentiate

viral from bacterial pneumonias based on the chest radiograph alone.

CRP concentration measured from blood is a readily available[35,39] inexpensive test. With recent availability of rapid CRP tests we can readily use in emergency settings[35,40]. CRP may become valuable diagnostic tool in the initial evaluation of febrile young children for occult serious bacterial infection and determine which children need additional diagnostic tests and antibiotic therapy.

SUMMARY: The study demonstrates that CRP concentration is better than other tests in predicting occult serious bacterial infection in febrile young children. CRP concentration is both sensitive and specific than WBC and ANC.

CONCLUSION

1. Semiquantitative CRP is useful in predicting occult serious bacterial infection in children between 1 month to 36 months.

2. CRP is considered to be better predictive test than total white blood cell count and absolute neutrophil count.

3. CRP and ANC or CRP, ANC &WBC combination is more useful than isolated CRP concentration.

4. CRP determines more selective strategy for children with SBI for additional diagnostic studies and appropriate antibiotic therapy.

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PROFORMA

Name

Age

Sex

Address

OP/IP Number

SYMPTOMS

History

Duration of fever

SIGNS

Temperature recording

Clinical examination

Examination of other systems

INVESTIGATIONS

Blood

Total WBC count

Absolute neutrophil count

Peripheral smear

Eythrocyte sedimentation rate

CRP

Blood culture

Urine analysis

Urine culture

Chest x ray

CSF analysis if needed